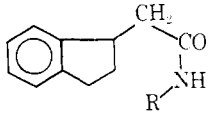
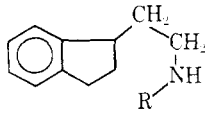
TABLE I
1-ALKYLACETAMIDOINDANS (II)



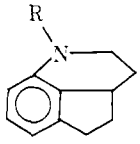
R	Mp, °C	Bp, °C (mm)	Formula
Me	72–73		$C_{12}H_{15}NO$
Et	69–71		$C_{13}H_{17}NO$
n-Pr		185–187 (1)	$C_{14}H_{19}NO$
n-Bu		173–175 (0.8)	$C_{15}H_{21}NO$

TABLE II
1-ALKYLAMINOETHYLINDANS (III)



R	Bp, °C (mm)	Formula	λ_{max}, mμ	ε × 10^{-2}
Me	90–92 (0.5)	$C_{12}H_{17}N$	266, 273	11.43, 12.43
Et	104–105 (0.6)	$C_{13}H_{19}N$	266, 273	11.89, 13.03
n-Pr	125–127 (1)	$C_{14}H_{21}N$	266, 273	11.42, 9.88
n-Bu	135–137 (0.8)	$C_{15}H_{23}N$	266, 273	11.63, 10.18

TABLE III
1,2,3,3a-TETRAHYDRO-1-ALKYLCYCLOPENTA[*de*]QUINOLINES (VI)



R	Bp, °C (mm)	Formula	λ_{max}, mμ	ε × 10^{-2}
Me	83–85 (0.5)	$C_{12}H_{15}N$	265	67.59
Et	114–115 (0.6)	$C_{13}H_{17}N$	268	64.15
n-Pr	120–122 (0.8)	$C_{14}H_{19}N$	267	38.04
n-Bu	107–109 (1)	$C_{15}H_{21}N$	262	31.72

the mixture was heated at 70–80° with stirring for 0.5 hr in the presence of light. It was then cooled and poured onto ice, basified with NaOH under cooling, extracted (PhH), and tosylated with TsCl (6 g, 31.6 mmoles) in PhH solution under stirring at 5–8° in the beginning and later at 40° with simultaneous addition of 3 *N* NaOH (25 ml) to keep the mass alkaline. The PhH layer was separated out and the tertiary amine was repeatedly extracted (6 *N* HCl). The combined acid extracts were basified with NaOH under cooling, extracted (Et_2O), and dried (Na_2SO_4), and the base was distilled. The yield varied from 30–40%. The physical characteristics of VI are reported in Table III.

Acknowledgments.—The authors' thanks are due to the Council of Scientific and Industrial Research, New Delhi, India, for part financial support and to the Director, Central Drug Research Institute, Lucknow, India, for the amebicidal test report.

Antimalarials. 4-Substituted 1H-Pyrazolo[3,4-*b*]quinolines

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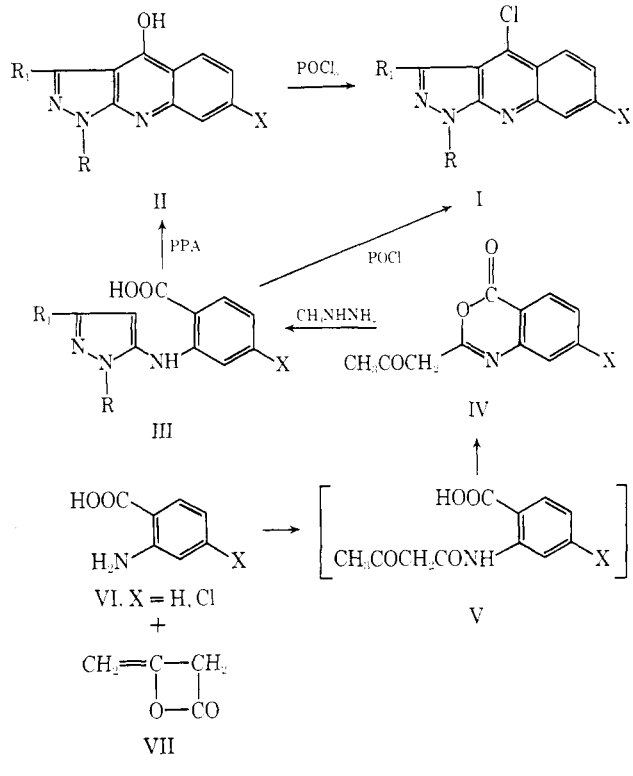
Pyrazole derivatives are known to possess various kinds of biological activity. For example, the pyrazolo[3,4-*b*]pyrimidine derivative, an isostere of caffeine, is indistinguishable from caffeine in its diuretic properties and is also a strong CNS stimulant.[1] 5-Aminopyrazolo[3,4-*b*]pyridines are vasodilators or cardiotonics.[2] 1-Substituted 3-dimethylaminoalkoxy-1H-indazoles show sedative, muscle relaxant, and antiinflammatory properties.[3] Several pyrazole derivatives, where the pyrazole ring is not fused with another ring, such as substituted aminopyrazoles, possess antiinflammatory, analgetic, antipyretic, adrenolytic, narcosis-potentiating, and antirheumatic activity.[4] Several derivatives of 1-phenyl-3-methyl-4-(substituted amino)-1H-pyrazolo[3,4-*b*]quinolines (anilino and substituted anilino)[5] and 1,3-dimethyl-1H-pyrazole[3,4-*b*]quinoline[6,7] have been prepared but not tested.

We were interested in combining the features of the pyrazole ring, a substituted quinoline, and an "antimalarial" side chain in one molecule for antimalarial testing. The key intermediate required was a 4-chloro-1H-pyrazolo[3,4-*b*]quinoline (I), in which the active Cl could be replaced with suitable amines expected to impart antimalarial activity to the final products. The method for preparing it is outlined in Scheme I.

SCHEME I



(1) P. Schmidt, K. Eichenberger, and M. Wilhelm, *Angew. Chem.*, **73**, 15 (1961); G. deStevens, "Diuretics," Academic Press, New York, N. Y., 1963, pp 21–23.

(2) CIBA Ltd., Netherlands Patents SW 359/66, 15786/66, 16738/66 (July 13, 1967); Netherlands Patents Report, Vol. 4, No. 29, 1967.

(3) G. Palazzo, G. Corsi, L. Baiocchi, and B. Silvestrini, *J. Med. Chem.*, **9**, 38 (1966).

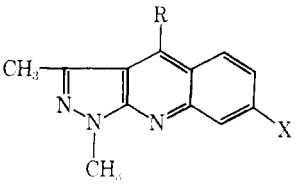
(4) E. Jucker, A. J. Lindenmann, and E. Rissi, U. S. Patent 3,041,342 (1962). For other references see K. Eichenberger, *et al.*, *Helv. Chim. Acta*, **48**, 524 (1965); *Naturwissenschaften*, **52**, 106 (1965); J. Druery and P. Schmidt, U. S. Patent 3,064,005 (1962); H. Snyder, U. S. Patent 3,293,261; (1966); *Chem. Abstr.*, **66**, 46424g (1967); J. B. Bocking, U. S. Patent 3,097,-210 (1963); Belgian Patent 612,971 (1962); D. E. Wright, U. S. Patent 3,102,890 (1963).

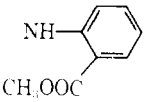
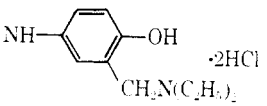
(5) A. Brack, *Ann.*, **681**, 105 (1965).

(6) G. Wolfrum, R. Puetter, H. G. Hanke, and K. H. Menzel, German Patent 1,152,421 (1963); *Chem. Abstr.*, **60**, 2945*f* (1964).

(7) G. Wolfrum, R. Puetter, H. G. Hanke, and K. H. Menzel, Belgian Patent 632,758 (1963); *Chem. Abstr.*, **61**, 756*e* (1964).

TABLE I



No.	X	R	Yield, %	Mp or bp (mm),[a] °C	Formula	Analyses
1	H	Cl	87.0	115–118		
2	H	OH	92.0	338–340		
3	H	$NH_2 \cdot HCl$	27.0	350	$C_{12}H_{13}ClN_4$	C, H, Cl, N
4	H	$NH(CH_2)_3N(CH_3)_2$	51.0	150–160 (0.001)[b]	$C_{17}H_{23}N_3$	C, H, N
5	H	$NH(CH_2)_3N(C_2H_5)_2$ CH_3	68.0	130–145 (0.001)	$C_{19}H_{27}N_3$	H, N; C[c]
6	H	$NHCH(CH_2)_3OH$ CH_3	55.0	103.5–105	$C_{17}H_{22}N_4O \cdot H_2O$	C, H, N
7	H	$NHCH(CH_2)_3N(C_2H_5)_2$	75.0	135–145 (0.001)	$C_{21}H_{31}N_3$	C, H, N
8	Cl	Cl	70.0	184–185	$C_{12}H_9Cl_2N_3$	C, H, N
9	Cl	NH_2	60.0	245–246	$C_{12}H_{11}ClN_4$	C, H, N
10	Cl	$NH(CH_2)_2N(CH_3)_2$	50.0	127–128	$C_{16}H_{20}ClN_3$	C, H, N
11	Cl	$NH(CH_2)_2N(C_2H_5)_2$	75.0	109–110.5	$C_{18}H_{24}ClN_3$	C, H, N
12	Cl	$NH(CH_2)_3N(C_2H_5)_2$	52.0	180–185 (0.001)	$C_{19}H_{26}ClN_3$	C, H, N
13	Cl	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	71.0	190–200 (0.001)	$C_{21}H_{30}ClN_3$	C, H, N
14	Cl		70.0	182–183.5	$C_{20}H_{17}ClN_4O_2$	C, H, N
15	Cl		77.0	294–296	$C_{23}H_{28}ClN_5O$	C, H, N

[a] All melting points are uncorrected. [b] Distillation was done in a Kugelrohr apparatus. [c] C: calcd, 70.12; found, 69.44.

Biological Tests.—Compounds **1–15** and the intermediates IV (X = H, Cl) and III (R = R_1 = CH_3; X = H, Cl) were tested for their antimalarial activity against *Plasmodium berghei* in mice by Dr. L. Rane of the University of Miami, Fla.[8]

The intermediates and the final compounds showed no appreciable antimalarial activity. Compounds **7** and **13**, which have the same side chain as chloroquine, showed a mean survival time of 7.2 and 9.6 days (control 6.0–6.5 days), respectively, at a dose of 320 mg/kg, and compound **15** showed a mean survival time of 11.2 days at a dose of 640 mg/kg. A minimum mean survival time of 13.0 days or more is required for the compound to qualify as being active and the animal (s) must live for 60 days or more when the drug can be called curative.

Experimental Section

The yields, melting points, and analyses for **1–15** are given in Table I.

2-Acetonylbenzoxazine (IV, X = H) and **N-(1,3-dimethyl-5-pyrazolyl)anthranilic acid (III, X = H)** were made according to the procedure of Puetter, *et al.*[9]

2-Acetonyl-7-chlorobenzoxazine (IV, X = Cl) was made by the same procedure as for IV (X = H), starting from 5-chloro-2-aminobenzoic acid and substituting PhCl as a solvent for CCl_4. The product was crystallized from THF; yield 50%, mp 186–188°. *Anal.* ($C_{11}H_8ClNO_3$) C, H, N.

4-Chloro-N-(1,3-dimethyl-5-pyrazolyl)anthranilic acid (III, X = Cl) was prepared in 60% yield by the same procedure as for III (X = H) and crystallized from EtOH–H_2O: mp 232–233°. *Anal.* ($C_{11}H_{12}ClN_3O_2$) H; C: calcd, 54.25; found, 53.78; N: calcd, 15.80; found, 15.24. None of the several other analyses carried out on this compound checked well. However, the subsequent compounds obtained from it analyzed satisfactorily.

4-Chloro-1,3-dimethyl-1H-pyrazolo[3,4-*b*]quinoline (1) and **1,3-dimethyl-4-hydroxy-1H-pyrazolo[3,4-*b*]quinoline (2)** were made according to the procedure of Wolfrum, *et al.*[6,7]

4,7-Dichloro-1,3-dimethyl-1H-pyrazolo[3,4-*b*]quinoline (8) was prepared by the procedure mentioned for **1** and was crystallized from $CHCl_3$.

4-Amino-1,3-dimethyl-1H-pyrazolo[3,4-*b*]quinoline (3).—A solution of 4-chloro-1,3-dimethyl-1H-pyrazolo[3,4-*b*]-quinoline (6.93 g, 0.03 mol) in 50 ml of PhOH was heated to 70° and $(NH_4)_2CO_3$ (6.0 g, 0.625 mol) was added to it portionwise with stirring over a period of 0.5 hr. The mixture was then heated at 120° for 2 hr, cooled, and poured into 450 ml of Et_2O. HCl gas was passed through the Et_2O solution and the precipitated salt was filtered, washed with a little H_2O, and crystallized from H_2O; yield 2.5 g.

4-Amino-7-chloro-1,3-dimethyl-1H-pyrazolo[3,4-*b*]quinoline (9) was prepared by the procedure described for **3**, except that the reaction mixture was poured into 10% NaOH solution and not Et_2O. The precipitated product was filtered and crystallized from EtOH to give a yellow solid.

4-Substituted Amino-1H-pyrazolo[3,4-*b*]quinolines (4–7, 10–14).—All of these derivatives were prepared by one general procedure exemplified by the preparation of 1,3-dimethyl-4-(4-diethylamino-1-methylbutylamino)-1H-pyrazolo[3,4-*b*]quinoline (**7**).

A solution of 4-chloro-1,3-dimethyl-1H-pyrazolo-[3,4-*b*]quinoline (8.0 g, 0.0346 mol), 2-amino-4-diethylaminopentane (10.0 g, 0.063 mol), and 50.0 g of PhOH was heated at 100° for 12 hr. The reaction mixture was cooled, poured into 2 *N* NaO, and extracted with three 150-ml portions of Et_2O. The Et_2O extracts were combined and extracted with three 100-ml portions of 10% AcOH. The AcOH solution was basified and extracted (Et_2O), and the extracts were dried (K_2CO_3), filtered, and con-

(8) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967)

(9) R. Puetter, G. Wolfrum, and H. G. Hanke, U. S. Patent 3,257,410 (1966).

centrated to an oil, which was distilled under high vacuum. Compound **6** solidified after the reaction mixture was poured into 2 *N* NaOH and left overnight and was crystallized from EtOH–H_2O. The same was the case with **14**, which was crystallized from DMF–H_2O. Compounds **10** and **11** solidified after the dried Et_2O extract was concentrated and were crystallized from EtOAc and petroleum ether (bp 30–60°), respectively.

7-Chloro-1,3-dimethyl-4-(3-diethylaminomethyl-4-hydroxyanilino)-1H-pyrazolo[3,4-*b*]quinoline (15).—A solution of 3-diethylaminomethyl-4-hydroxyaniline (5.7 g, 0.02 mol) in a minimum amount of H_2O was neutralized with dilute NaOH to congo red paper. To this was added 4,7-dichloro-1,3-dimethyl-1H-pyrazolo[3,4-*b*]quinoline (5.0 g, 0.02 mol) and 100 ml of ethoxyethanol. The mixture was refluxed for 4 hr. A clear solution formed after 2 hr and then a yellow solid separated. The reaction was cooled, and the yellow solid was filtered and crystallized from Me_2CO–H_2O.

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Febrifugine Antimalarial Agents. I. Pyridine Analogs of Febrifugine

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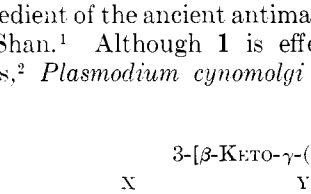
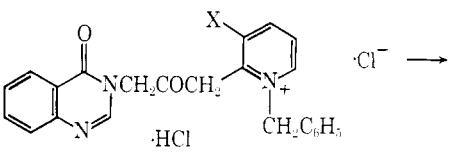
The alkaloid febrifugine (**1**) has been shown to be the active ingredient of the ancient antimalarial preparation Ch'ang Shan.[1] Although **1** is effective against avian malarias,[2] *Plasmodium cynomolgi* in monkeys,[3] and *Plasmodium berghei* in mice,[4] it has poor activity against *Plasmodium falciparum* and *Plasmodium vivax*;[4–6] in addition, it is a powerful emetic and has a low chemotherapeutic index.[4] Several analogs of **1**[7] showed an improved chemotherapeutic index against *Plasmodium lophurae* in ducks;[2] one analog was tested in limited clinical trails, but was ineffective against *P. vivax* and *P. falciparum*.

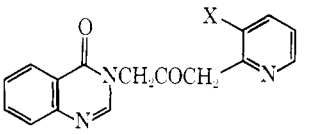


1

We have now prepared 3-[β-keto-γ-(3-hydroxy-2-pyridyl)propyl]-4-quinazolone (**3c**) (Table I), in which the piperidine ring of the side chain has been replaced by pyridine. Baker and McEvoy[8] synthesized the



2



3

a, X = H
b, X = OCH_3
c, X = OH

pyridinium derivative **2b**, and described hydrogenolysis of the corresponding free base to the methyl ether **3b** using Raney Ni catalyst. However, no attempt to prepare **3c** by cleavage of the MeO group was reported.

Working with the desoxy analog **2a**[8] as a model compound, we found that hydrogenolysis of the benzyl group could be effected smoothly over Pd–C, affording 3-[β-keto-γ-(2-pyridyl)propyl]-4-quinazolone (**3a**). The MeO derivative **2b** gave **3b** under identical conditions.

TABLE I
3-[β-KETO-γ-(3-SUBSTITUTED 2-PYRIDYL)PROPYL]-4-QUINAZOLONES

Compd	X	Yield, %	Mp, °C	Formula[c]
3a	H	59	209–212[a]	$C_{16}H_{13}N_3O_2 \cdot 2HCl \cdot H_2O$
3b	OCH_3	41	151–155[b]	$C_{17}H_{15}N_3O_3$
3c	OH	53	211–214 dec[a]	$C_{16}H_{13}N_3O_3 \cdot 2HCl \cdot 1.5H_2O$

[a] Washed with AcMe, Et_2O. [b] Recrystallized from MeOH; lit.[7] mp 157–158°. [c] All compounds were analyzed for C, H, N.

For the preparation of **3c**, the intermediate 1-benzyl-3-hydroxy-2-[β-keto-γ-(4-quinazolon-3-yl)propyl]pyridinium chloride hydrochloride (**2c**) was hydrogenolyzed over Pd–C.

Compounds **3a–c** were assayed against *P. berghei* in mice and *Plasmodium gallinaceum* in chicks.[9] No antimalarial activity was observed.

Experimental Section

Melting points were determined on a Thomas–Hoover "Uni-Melt" capillary melting point apparatus and are not corrected. The ir and nmr spectra were as expected.

1-Benzyl-3-hydroxy-2-[β-keto-γ-(4-quinazolon-3-yl)propyl]-pyridinium Chloride Hydrochloride (2c).—A solution of **2b** (13.7 g, 0.029 mole) in 573 ml of 48% aqueous HBr was refluxed for 18 hr. After cooling, the solution was evaporated to dryness *in vacuo*. A saturated solution of $NaHCO_3$ was added to the residue; the resulting mixture was extracted ($CHCl_3$), and the

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(2) R. Hewitt, E. R. Gill, W. S. Wallace, and J. H. Williams, *Am. J. Trop. Med. Hyg.*, **1**, 768 (1952).
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(5) G. R. Coatney, W. C. Cooper, W. B. Culwell, W. C. White, and C. A. Imboden, Jr., *J. Natl. Malaria Soc.*, **9**, 183 (1950).
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(7) B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy, and J. H. Williams, *J. Org. Chem.*, **17**, 141, 149, 157, 164 (1952); **18**, 133, 138 (1953).
(8) B. R. Baker and F. J. McEvoy, *ibid.*, **20**, 118 (1955).
(9) The screening tests were carried out at the University of Miami, Miami, Fla., under the direction of Dr. L. Rane. Details of the mouse screen with *P. berghei* have been published [T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967)].